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(54) Title: METHOD OF TREATING DIABETES AND DIABETES-RELATED DISORDERS

(57) Abstract: This invention relates to a method of treating diabetes and diabetes-related disorders. Specifically, the method of the present invention relates to administering a single compound that lowers blood glucose levels, lowers serum triglyceride levels, and increases serum high density lipoproteins (HDL) levels thereby providing a treatment option for individuals afflicted with a metabolic disorder such as diabetes mellitus, insulin resistance, impaired glucose tolerance, and dyslipidemia.

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METHOD OF TREATING DIABETES AND DIABETES-RELATED DISORDERS

[001] This application claims benefit of U.S. Provisional Application Serial No. 60/454,281, filed March 13, 2003, the contents of which are incorporated herein by reference in their entirety.

FIELD OF THE INVENTION

[002] This invention relates to a method of treating diabetes and diabetes-related disorders. Specifically, the method of the present invention relates to administering a single compound that lowers blood glucose levels, lowers serum triglyceride levels, and increases serum high density lipoproteins (HDL) levels thereby providing a treatment option for individuals afflicted with a metabolic disorder such as diabetes mellitus, insulin resistance, impaired glucose tolerance, and dyslipidemia.

BACKGROUND OF THE INVENTION

[003] Diabetes is characterized by impaired glucose metabolism manifesting itself among other symptoms by an elevated blood glucose level in the diabetic patient. Underlying defects lead to the classification of diabetes into two major groups: type 1 diabetes, or insulin dependent diabetes mellitus (IDDM), which arises when patients lack β-cells (β-cells produce insulin in the pancreatic gland), and type 2 diabetes, or non-insulin dependent diabetes mellitus (NIDDM), which occurs in patients with an impaired β-cell function and alterations in insulin action.

[004] Type 2 diabetes, is the more common form of diabetes, with 90-95% of hyperglycemic patients experiencing this form of the disease. In type 2 diabetes, there appears to be a reduction in the pancreatic β-cell mass, several distinct defects in insulin secretion, or a decrease in tissue sensitivity to insulin. The symptoms of this form of diabetes include fatigue, frequent urination, thirst, blurred vision, frequent infections and slow healing of sores, diabetic nerve damage, retinopathy, and renal disease.

[005] Resistance to the metabolic actions of insulin is one of the key features of type 2 diabetes. Insulin resistance is characterized by impaired uptake and utilization of glucose in insulin-sensitive target organs, for example, adipocytes and skeletal muscle, and by impaired inhibition of hepatic glucose output. The functional insulin deficiency and the failure of insulin to suppress hepatic glucose output results in fasting hyperglycemia. Pancreatic β-cells compensate for insulin resistance by secreting increased levels of insulin. However, the β-cells are unable to maintain this high output of insulin, and eventually, the glucose-induced insulin secretion falls, leading to the deterioration of

glucose homeostasis and to the subsequent development of overt diabetes. Most patients with type 2 diabetes suffer not only from hyperglycemia, but also diabetic dyslipidemia that includes elevated triglycerides and low density lipoprotein (LDL), and decreased high density lipoprotein (HDL) levels. It is well known that lowering plasma glucose will significantly reduce microvascular complications, but does not prevent macrovascular disease, the main cause of death in patients with type 2 diabetes (Haffner, et al., N. Engl. J. Med. 339:229, 1998; Goldberg, J. Clin. Endocrinol. Metabol 86:965-971, 2001; UK Prospective Diabetes Study (UKPDS) Group, Lancet 352:837, 1998; UK Prospective Diabetes Study (UKPDS) Group, Lancet 352:854, 1998). Improving diabetic dyslipidemia, that is, lowering triglycerides and/or LDL, and raising HDL levels, significantly reduces the progression of macrovascular complications in patients with type 2 diabetes (Diabetes Atherosclerosis Intervention Study (DAIS) Investigators, Lancet 357:905-910, 2001; Tan, et al., Atherosclerosis 154:469-474, 2001; Frost, et al., Amer. J. Cardiol. 87:44-48, 2001). New therapies for type 2 diabetes are now expected to treat both hyperglycemia and diabetic dyslipidemia.

[006] Hyperinsulinemia is also linked to insulin resistance, hypertriglyceridemia, and increased plasma concentration of low-density lipoproteins. The association of insulin resistance and hyperinsulinemia with these metabolic disorders has been termed "Syndrome X," and has been strongly linked to an increased risk of hypertension and coronary artery disease.

[007] Despite the presence of some pharmaceuticals that are used to treat these diseases, there remains a need for new pharmaceuticals that are both safe and effective agents for the treatment of disease. Current therapies focus on insulin sensitivity and glucose control but do not specifically address diabetic dyslipidemia.

[008] Type 1 diabetic patients are currently treated with insulin, while the majority of type 2 diabetic patients are treated with agents that stimulate β-cell function or with agents that enhance the tissue sensitivity of these patients towards insulin. Over time, almost one-half of type 2 diabetic subjects lose their response to these agents and then, must be placed on insulin therapy.

[009] The drugs presently used to treat type 2 diabetes include, for example, alpha-glucosidase inhibitors which reduce the excursion of postprandial glucose by delaying the absorption of glucose from the gut. These drugs are safe and provide treatment for mild to moderately affected diabetic subjects. However, gastrointestinal side effects have been reported.

[010] Insulin sensitizers such as rosiglitazone and pioglitazone activate the peroxisome proliferator activated receptor (PPAR) gamma receptor and modulate the activity of a set of genes that have not been well characterized. Although effective, these drugs are associated with edema and do not specifically address macrovascular component of diabetic complications.

[011] Insulin secretagogues such as sulfonylureas (SFUs), and other agents that act by the ATP-dependent K+ channel, are standard therapy for type 2 diabetics that have mild to moderate fasting glycemia. SFUs have limitations that include a potential for inducing hypoglycemia, weight gain, and high primary and secondary failure rates. Ten to 20% of initially treated patients fail to show a significant treatment effect (primary failure). Secondary failure is demonstrated by an additional 20-30% loss of treatment effect after six months on SFU treatment. Insulin treatment is required in 50% of the SFU responders after 5-7 years of therapy (Scheen et al., Diabetes Res. Clin. Pract. 6:533-543, 1989).

[012] Metformin is a biguanide that lowers blood glucose by decreasing hepatic glucose output and increasing peripheral glucose uptake and utilization. The drug is effective at lowering blood glucose in mildly and moderately affected subjects and does not have the side effects of weight gain or the potential to induce hypoglycemia. However, metformin has a number of side effects including gastrointestinal disturbances and lactic acidosis. Metformin is contraindicated in diabetics over the age of 70 and in subjects with impairment in renal or liver function. Finally, metformin has the same primary and secondary failure rates as the SFUs.

[013] Insulin treatment is generally instituted after diet, exercise, and oral medications have failed to adequately control blood glucose. This treatment is by an injectable and it can produce hypoglycemia as well as weight gain.

[014] Because of the problems with current treatments, new therapies to treat type 2 diabetes are needed. In particular, new treatments to address both hyperglycemia and dyslipidemia are needed. Such new drugs should have the following characteristics: dependence on glucose for promoting insulin secretion, that is, produce insulin secretion only in the presence of elevated blood glucose; correct diabetic dyslipidemia, for example, increase HDL levels and lower triglyceride and LDL levels; and minimal primary and secondary failure rates.

[015] Compounds of the insulin sensitizer category are involved in energy homeostasis. Insulin sensitizers improve glucose regulation in human type 2 diabetic patients and alleviate microvascular complications of type 2 diabetes, however, these medications

have little to no effect on macrovascular complications. Fibrates, such as fenofibrate, and statins are another type of medication used to treat patients with type 2 diabetes to control macrovascular complications of diabetes. Fibrates are used to lower serum triglycerides, while statins are used to lower LDL levels in patients with diabetic dyslipidemia.

[016] Currently, there exists a need for a holistic approach for the treatment of type 2 diabetes. One potential therapeutic approach to such treatment is the use of compounds that can improve glucose control and correct diabetic dyslipidemia, a major underlying cause of macrovascular complications and cause of death in a significant number of patients with diabetes. In particular, a therapy that can achieve the following end points in a single compound is needed: 1) alleviate hyperglycemia; 2) increase serum HDL levels; and 3) lower serum triglycerides. Such a compound would be more beneficial to a patient with type 2 diabetes or Syndrome X with dyslipidemia because it would possess triple activity (i.e., lower glucose and serum triglyceride levels, and increase HDL levels) while minimizing potential side effects that could come from administration of multiple compounds to treat these conditions.

SUMMARY OF THE INVENTION

[017] The present invention relates to a method of treating diabetes and diabetes-related disorders by administering to a subject in need a single compound with triple activity, that is, a compound which lowers blood glucose, increases serum HDL levels, and decreases serum triglyceride levels.

[018] Diabetes-related disorders include hyperglycemia, hyperinsulinemia, impaired glucose tolerance, impaired fasting glucose, dyslipidemia, hypertriglyceridemia, Syndrome X, insulin resistance, obesity, atherosclerotic disease, hyperlipidemia, hypercholesteremia, low HDL levels, hypertension, cardiovascular disease, cerebrovascular disease, peripheral vessel disease, lupus, polycystic ovary syndrome, carcinogenesis, and hyperplasia.

[019] The method of the present invention may be used to treat mammals such as rodents, primates including humans, sheep, canines, felines, bovines, and swine. In another embodiment, the method of the present invention comprises administering to a subject in need a compound which has glucose-lowering activity, triglyceride-lowering activity, and increases HDL levels in combination with one or more hypoglycemic agents.

[020] In a further embodiment, the method of the present invention comprises

administering to a subject in need a compound which has glucose-lowering activity, triglyceride-lowering activity, and increases HDL levels in combination with one or more agents including HMG CoA reductase inhibitors, bile acid binding agents, fibric acid derivatives, agents that regulates hypertension, or agents that regulates body weight.

[021] The present invention also relates to a pharmaceutical composition comprising a compound which has glucose-lowering activity, triglyceride-lowering activity, and increases HDL levels with a pharmaceutically acceptable carrier. This pharmaceutical composition may also include one or more hypoglycemic agents, HMG CoA reductase inhibitors, bile acid binding agents, fibric acid derivatives, agents that regulates hypertension, or agents that regulates body weight.

DETAILED DESCRIPTION OF THE INVENTION

[022] It is to be understood that this invention is not limited to the particular methodology, protocols, cell lines, animal species or genera, and reagents described and as such may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the present invention which will be limited only by the appended claims.

[023] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood to one of ordinary skill in the art to which this invention belongs.

[024] All publications and patents mentioned herein are hereby incorporated herein by reference for the purpose of describing and disclosing, for example, the methodologies that are described in the publications which might be used in connection with the presently described invention.

[025] The method of the present invention may be effective in the treatment of type 2 diabetes, as well as for a number of diabetes-related disorders, such as hyperglycemia, hyperinsulinemia, impaired glucose tolerance, impaired fasting glucose, dyslipidemia, hypertriglyceridemia, Syndrome X, insulin resistance, obesity, and in the treatment of atherosclerotic disease, hyperlipidemia, hypercholesteremia, low HDL levels, hypertension, cardiovascular disease (including atherosclerosis, coronary heart disease, coronary artery disease, and hypertension), cerebrovascular disease and peripheral vessel disease; and for the treatment of lupus, polycystic ovary syndrome, carcinogenesis, and hyperplasia.

[026] Obesity is an excessive accumulation of adipose tissue. Excess adipose tissue is associated with the development of serious medical conditions, for example, type 2 diabetes, hypertension, coronary artery disease, hyperlipidemia, obesity, and certain malignancies. The adipocyte may also influence glucose homeostasis through the production of tumor necrosis factor α (TNFα) and other molecules.

[027] Atherosclerotic disease is a major cause of death in type 2 diabetes and is known to be caused by a number of factors, for example, hypertension, diabetes, low levels of HDL, and high levels of LDL. Atherosclerotic disease includes cardiovascular disease, coronary heart disease (CHD), cerebrovascular disease, and peripheral vessel disease. Coronary heart disease includes CHD death, myocardial infarction, and coronary revascularization. Cerebrovascular disease includes ischemic or hemorrhagic stroke, and transient ischemic attacks.

[028] Accordingly, despite the presence of some pharmaceuticals that are used to treat these diseases, there remains a need for new pharmaceuticals that are both safe and effective agents for the treatment of these diseases.

[029] Particularly useful compounds are those with efficacy in lowering blood glucose levels and serum triglyceride levels, and raising serum HDL cholesterol levels, that is, a compound which possesses triple activity.

[030] Furthermore, this compound with triple activity may be administered alone or in combination with one or more additional hypoglycemic agents. Combination therapy includes administration of a single pharmaceutical dosage formulation which contains a compound with triple activity and one or more additional hypoglycemic agent, as well as administration of a compound with triple activity and each additional hypoglycemic agents in its own separate pharmaceutical dosage formulation. For example, a compound with triple activity and hypoglycemic agent may be administered to a subject together in a single oral dosage composition such as a tablet or capsule, or each agent may be administered in separate oral dosage formulations.

[031] Where separate dosage formulations are used, a compound with triple activity and one or more additional hypoglycemic agents may be administered at essentially the same time (e.g., concurrently) or at separately staggered times (e.g., sequentially).

[032] For example, a compound with triple activity may be administered in combination with one or more of the following additional hypoglycemic agents: insulin; biguanidines such as metformin or buformin; sulfonylureas such as acetohexamide, chloropropamide, tolazamide, tolbutamide, glyburide, glipizide, glyclazide; or any other insulin secretagogue

such as, for example, repaglinide and nateglinide; α-glycosidase inhibitors such as acarbose, voglibose, or miglitol; or β_3-adrenoreceptor agonists such as CL-316,243.

[033] Also, a compound with triple activity may be used in combination with HMG Co-A reductase inhibitors (statins), bile acid binding resin, or fibric acid derivatives to improve the lipid profile of subjects with dyslipidemia and insulin resistance. Furthermore, a compound with triple activity may also be used in combination with agents that regulate hypertension (e.g., inhibitors of angiotension converting enzyme (ACE), β-blockers, calcium channel blockers) and body weight of subjects with insulin resistance or type 2 diabetes.

[034] The following compounds are presented to illustrate the invention described herein, but should not be construed as limiting the scope of the invention in any way. The particular process to be utilized in the preparation of these compounds depends upon the specific compound desired. Such factors as the selection of a specific moiety, and the specific substituents possible at various locations on the molecule, all play a role in the path to be followed in the preparation of the compounds of this invention. Those factors are readily recognized by one of ordinary skill in the art.

ABBREVIATIONS AND ACRONYMS

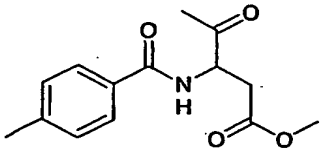
[035] When the following abbreviations are used herein, they have the following meaning:

Celite®	diatomaceous earth filter agent, ®Celite Corp.
CH_2Cl_2	methylene chloride
CI-MS	chemical ionization mass spectroscopy
conc	concentrated
DCM	dichloromethane
DMAP	4-(*N,N*-dimethylamino)pyidine
ee	enantiomeric excess
EtOAc	ethyl acetate
EtOH	ethanol (100%)
EtSH	ethanethiol
Et_2O	diethyl ether
Et_3N	triethylamine
HPLC	high performance liquid chromatography
IPA	isopropylamine

rt	room temperature
THF	tetrahydrofuran
TLC	thin layer chromatography
TMAD	N,N,N',N'-tetramethylethylenediamine

[036] **EXAMPLE 1**

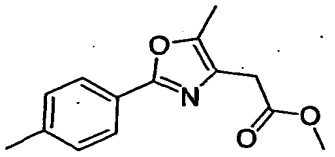
Preparation of methyl 3-[(4-methylbenzoyl)amino]-4-oxopentanoate



[037] To a suspension of L-aspartic acid β-methyl ester hydrochloride (Sigma, 250 g, 1.36 mol) in chilled (<5°C) CH_2Cl_2 (4 L) was added Et_3N (440 g, 4.35 mol) in a steady flow followed by a slow addition of Me_3SiCl (324 g, 2.99 mol). The mixture was warmed to 25°C and stirred for one hour, cooled again (< 10°C), and *p*-toluoyl chloride (205 g, 1.36 mol) was added dropwise. The mixture was allowed to warm to ambient slowly with stirring for 16 hours. The reaction mixture was then diluted with CH_2Cl_2 (500 mL) and washed with 1N HCl (500 mL), brine (500 mL), and dried over Na_2SO_4. The resultant amide product (310 g, 91%), a white solid, was obtained after solvent removal and drying under vacuum. It was then dissolved in pyridine (1.25 L) and DMAP (5 g) was added. Acetic anhydride (840 mL) was added slowly and then the reaction was heated at 90°C for 2 hours. The cooled solution was poured into 7 L ice water and extracted with 6 liters of EtOAc. The organic layer was washed with 2N HCl (3 x 1 L) and 1N NaOH (1 L), dried over $MgSO_4$ and concentrated to afford the title compound as a white solid (301 g, 93%).

[038] **EXAMPLE 2**

Preparation of methyl [5-methyl-2-(4-methylphenyl)-1,3-oxazol-4-yl]acetate

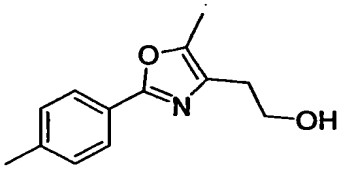


[039] The intermediate prepared in Example 1 (280 g, 1.06 mol) was dissolved in acetic anhydride (650 mL) followed by slow addition of conc. H_2SO_4 (60 mL). The pot temperature reached 80°C. The reaction was then held at 85°C for 1 hour, cooled, and the acetic anhydride removed *in vacuo*. The residue was poured into ice water (2 L) and extracted with EtOAc (4 L total). The organic layer was then stirred with 1 N NaOH (500

mL) for 1 hour, separated, then dried with $MgSO_4$ and concentrated to afford the title ester as a clear oil (223 g, 87%), which slowly solidified to a white solid.

[040] **EXAMPLE 3**

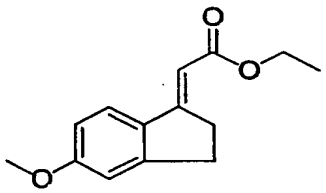
Preparation of 2-[5-methyl-2-(4-methylphenyl)-1,3-oxazol-4-yl]ethanol



[041] The oxazole ester prepared in Example **2** (300 g, 1.22 mol) was dissolved in THF (2.7 L) and solid $LiBH_4$ (26.6 g, 1.22 mol) was added in 5-g portions while maintaining temperature below 45°C. Reaction was complete within an hour after addition. Solvent was reduced to half volume and then poured into ice water (3 L). The mixture was then acidified by slowly adding 1 N HCl (1 L). A white precipitate formed and was collected by filtration and oven dried over P_2O_5 to give the desired oxazole ester (214 g, 83%).

[042] **EXAMPLE 4**

Preparation of ethyl (5-methoxy-2,3-dihydro-1*H*-inden-1-ylidene)ethanoate

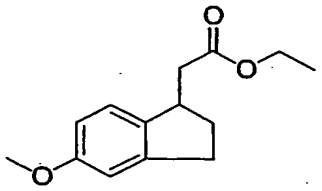


[043] To a solution of 5-methoxyindanone (150 g, 0.91 mol) in anhydrous tetrahydrofuran (4.5 L), was added zinc (30 mesh, 103.64 g, 1.59 mol) and copper(I) chloride (4.53 g, 0.045 mol). The suspension was stirred under argon atmosphere and refluxed for 15 minutes; approximately a 25% portion of ethyl bromoacetate (133 mL, 1.18 mol) was added to the refluxing mixture in a slow dropwise fashion. After allowing to cool and stirring overnight at rt, TLC showed the presence of desired product, indicating the formation of reactive zinc species. The remainder of ethyl bromoacetate was added dropwise; an exotherm was observed (internal temperature increased to 35°C). After 4 hours, TLC showed complete reaction. After the solids settled to the bottom of the flask, the liquid was siphoned off leaving a small amount behind to cover the solids. The flask was re-charged with 5-methoxyindanone (157.6 g, 1.86 mol total), anhydrous tetrahydrofuran (4.5 L), and zinc (80.92 g, 2.73 mol total). Ethyl bromoacetate (140 mL, 2.36 mol total) was added dropwise. An exotherm was observed (internal temperature

increased to 35°C). When the stirred mixture cooled to rt, TLC showed the reaction to be complete. The solids were allowed to settle and the liquid was siphoned off. The combined reaction solutions were concentrated *in vacuo* to a volume of ~ 2L. The liquid was then poured into sufficient 1N aqueous hydrochloric acid (cooled in ice water) to bring the pH to 1. The product was extracted with ethyl acetate (2 x 1 L, 1 x 500 mL). The combined extracts were washed with water, brine (1 L each), dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford a dark red oil which solidified gradually (438.3 g; theoretical yield = 432 g). ^{1}H NMR ($CDCl_3$): δ 7.5 (d, 1H), 6.8 (m, 2H), 6.2 (t, 1 H), 4.2 (q, 2H), 3.8 (s, 3H), 3.3 (m, 2H), 3.0 (t, 2H), 1.3 (t, 3H). MS (CI) *m/z* 233 $[M+H]^+$.

[044] **EXAMPLE 5**

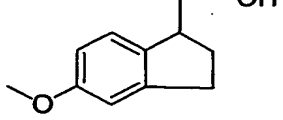
Preparation of ethyl (5-methoxy-2,3-dihydro-1*H*-inden-1-yl)acetate



[045] The crude product of Example 4 was dissolved in absolute ethanol (2.6 L) and hydrogenated at 40 psi of hydrogen over 10% palladium on carbon (21.6 g). Filtration through Celite and concentration of the filtrate afforded 433.3 g of brown oil (99% yield for 2 steps). ^{1}H NMR ($CDCl_3$): δ 7.1 (dd, 1H), 6.8 (d, 1H), 6.7 (dd, 1H), 4.2 (q, 2H), 3.8 (s, 3H), 3.5 (m, 1H), 2.9 (m, 2H), 2.7 (dd, 1H), 2.4 (m, 2H), 1.7 (m, 1H), 1.3 (t, 3H). MS (CI) *m/z* 235 $[M+H]^+$.

[046] **EXAMPLE 6**

Preparation of (5-methoxy-2,3-dihydro-1*H*-inden-1-yl)acetic acid

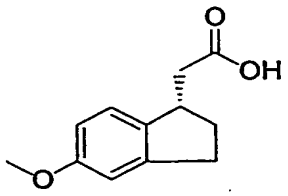


[047] To a solution of the crude ester (416 g, 1.77 mol) prepared in Example 5 in 1 L EtOH, was added a solution of NaOH (142 g, 3.54 mol) in 1500 mL of water. The cloudy reaction mixture was heated to reflux, during which time the color changed to dark red, and the reaction became homogeneous. After 1 hour, the reaction was cooled to rt, and the EtOH was removed under reduced pressure. The basic aqueous layer was washed

with Et_2O (3 x 500 mL), then acidified with conc. HCl to pH ~4 upon which an oil residue formed. The mixture was extracted with Et_2O (4 x 500 mL). The combined extracts were washed with water (2 x 300 mL), brine, then dried over Na_2SO_4. Filtration and evaporation of solvent under reduced pressure gave the title compound (305 g, 83%) as a yellow solid after overnight drying under vacuum. ^1H NMR ($CDCl_3$) δ 7.34(d, 1H), 6.71(s, 1H), 6.65(dd, 1H), 3.71(s, 3H), 3.47(m, 1H), 2.80(m, 3H), 2.35(m, 2H), 1.71(m, 1H). MS (CI) *m/z* 207 $[M+H]^+$.

[048] **EXAMPLE 7**

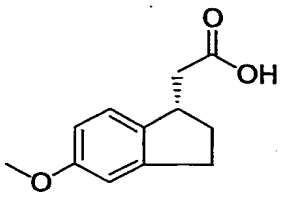
Preparation of [(1*S*)-5-methoxy-2,3-dihydro-1*H*-inden-1-yl]acetic acid



[049] To a solution of the acid (341.0 g, 1.65 mol) prepared in Example **6** in 8.2 L reagent grade acetone, was added *(S)*-(-)-α-methylbenzylamine (223.8 mL, 1.74 mol) dropwise at rt with stirring. A thick white precipitate formed during the addition. An additional 500 mL acetone was added and stirring continued for 1 hour. The solids were collected by filtration, washed with 300 mL acetone, and dried under suction. The solids were then suspended in acetone (8.2 L) and warmed to reflux until all solids dissolved. The solution was cooled slowly overnight, during which time a white precipitate formed. The suspension was cooled to 0°C, then filtered, and the solids were washed with 500 mL acetone. After drying under suction, a sample analyzed by HPLC showed 95% *ee*. The recrystallization process was repeated as above using 6.7 L acetone. HPLC analysis showed 99% *ee*. After drying under suction, 192 g salt were obtained. The salt was suspended in 2 L EtOAc and 1 L of 1 N HCl solution, and shaken in a separatory funnel, whereupon the salt dissolved. The organic layer was separated, washed with 1 N HCl (500 mL), water (2 x 300 mL), and brine, then dried over Na_2SO_4. The solvent was evaporated under reduced pressure, giving an oil which soon solidified. The title product (120.5 g, 35%) was obtained as an off-white solid after vacuum drying. ^1H NMR ($CDCl_3$) δ 7.10(d, 1H), 6.79(d, 1H), 6.73(dd, 1H), 3.79(s, 3H), 3.55(m, 1H), 2.89(m, 2H), 2.79(dd, 1H), 2.46(dd, 1H), 2.43(m, 1H), 1.80(m, 1H). MS (ESI) *m/z* 207 $[M+H]^+$.

[050] **EXAMPLE 8**

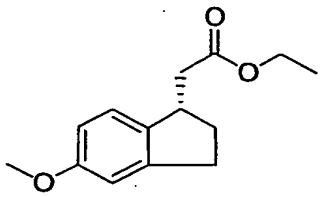
Preparation of [(1*S*)-5-methoxy-2,3-dihydro-1*H*-inden-1-yl]acetic acid



[051] As an alternative to Example 7, the title compound may also be prepared via an enzymatic process. Thus, a cloudy mixture of the crude ester (500.0 g, 2.13 mol; 87% pure as determined by HPLC) prepared in Example 5, in 1 L reagent grade acetone, 2.5 L phosphate Buffer (pH 7.0, 0.05 M) and 2.5 L deionized water was treated in one portion with Amano Lipase PS (150 g), and the mixture stirred efficiently at rt overnight. HPLC analysis of an aliquot (homogeneous aliquot prepared by dissolving aliquot in IPA followed by filtration) showed one peak corresponding to unreacted R-ester and another peak corresponding to desired S-acid. Trace amounts of S-ester and R-acid were noted. 2 N HCl (500 mL, ensure a pH ~2) was added in one portion to the reaction and stirred for 20 minutes. The mixture was filtered and the solids were washed with EtOAc (2 x 500 mL), then water (500 mL). The combined filtrates were further diluted with 1 L EtOAc, and the layers stirred together vigorously. Stirring was stopped and the layers allowed to separate. Emulsions were noted, but could be broken with the addition of solid NaCl and stirring. The aqueous layer was removed, then extracted with EtOAc (3 x 1 L) in the same fashion. The combined organic extractions were washed with water (4 x 500 mL), then with brine. The resulting organic layer was extracted with a 5% Na_2CO_3 solution (8 x 500 mL). HPLC analysis of the organic layer showed that it contained none of the S-enantiomer acid. The combined Na_2CO_3 extracts were washed with EtOAc (2 x 1 L), then acidified to pH ~2 by the addition of 2N HCl. A white solid precipitated, accompanied by CO_2 evolution. The mixture was extracted with EtOAc (3x1 L). The combined extracts were washed with water (2x1 L) and brine, then dried over Na_2SO_4. HPLC analysis of this solution showed the material was 98% *ee*. The solvent was evaporated under reduced pressure, giving an oil which soon solidified. The title product (172.9 g) was obtained as an off-white solid after vacuum drying. This material was recrystallized from boiling hexanes (8.8 L). After overnight cooling, light yellow needles were collected via filtration, washed with hexanes (200 mL), and dried under suction. The title product (146.9 g, 38% from crude starting ester) was obtained as light yellow needles after vacuum drying. ^1H NMR results as above.

[052] **EXAMPLE 9**

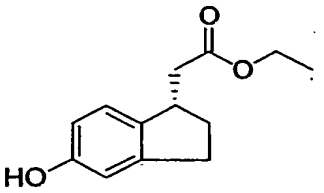
Preparation of ethyl [(1*S*)-5-methoxy-2,3-dihydro-1*H*-inden-1-yl]acetate



[053] To a solution of the acid (305 g, 1.48 mol) prepared in either Example **7** or **8** in 4.8 L of absolute EtOH at rt under argon, was added chlorotrimethylsilane (413 mL, 3.25 mol) dropwise. An approximate 5°C rise in temperature was noted during the addition. The reaction was stirred overnight. EtOH was evaporated under reduced pressure, giving a bi-phasic liquid mixture. This was diluted in 500 mL ice-water, then extracted with EtOAc (2 x 750 mL). The combined extracts were washed with water (3 x 300 mL), then with saturated $NaHCO_3$ (200 mL). The organic was washed once more with water (300 mL), then brine, and dried over Na_2SO_4. The title compound (354 g, 102%) was obtained as a light yellow oil after solvent removal and vacuum drying. ^1H NMR ($CDCl_3$) δ 7.07(d, 1H), 6.78(d, 1H), 6.71(dd, 1H), 4.18(q, 2H), 3.78(s, 3H), 3.52(m, 1H), 2.89(m, 2H), 2.72(dd, 1H), 2.37(o, 2H), 1.74(m, 1H), 1.28(t, 3H). MS (CI) *m/z* 235 $[M+H]^+$.

[054] **EXAMPLE 10**

Preparation of ethyl [(1*S*)-5-hydroxy-2,3-dihydro-1*H*-inden-1-yl]acetate

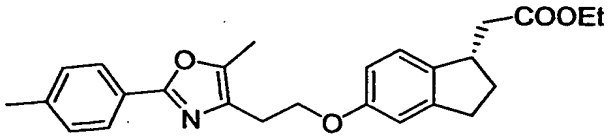


[055] To a cold solution (ice water bath) of the compound (346 g, 1.48 mol) prepared in Example **9** in 4.2 L CH_2Cl_2, was added $AlCl_3$ (984.6 g, 7.38 mol) portionwise under argon such that the reaction temperature was maintained below 10°C. The light brown suspension was stirred 10 minutes, then EtSH (546 mL, 7.38 mol) was added dropwise at such a rate that the reaction temperature was maintained below 5°C. After 2.5 hours of stirring below 10°C, the reaction mixture was slowly poured into 6 L of ice water with strong agitation. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 1 L). The combined CH_2Cl_2 layers were washed with water (2 x 1 L), then dried over Na_2SO_4. The solvent was removed under reduced pressure, giving a brown oil, which was filtered through a pad of silica gel (eluted with 0-10% EtOAc/Hexanes). Fractions were collected and the title compound (314 g, 96%) was

obtained as a thick yellow oil after solvent removal and vacuum drying. ^{1}H NMR ($CDCl_3$) δ 6.92(d, 1H), 6.62(d, 1H), 6.55(dd, 1H), 4.10(q, 2H), 3.43(q, 1H), 2.75(m, 2H), 2.64(dd, 1H), 2.31(dd, 1H), 2.29(m, 1H), 1.67(m, 1H), 1.20 (t, 3H). MS (CI) *m/z* 221 $[M+H]^+$.

[056] **EXAMPLE 11**

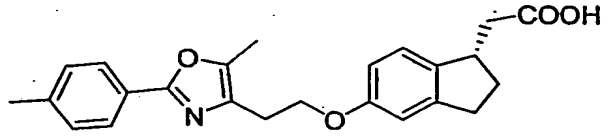
Preparation of ethyl 2-{(1*S*)-5-{2-[5-methyl-2-(4-methylphenyl)(1,3-oxazol-4-yl)]ethoxy}indanyl)acetate



[057] A suspension of the ethyl [(1*S*)-5-hydroxy-2,3-dihydro-1*H*-inden-1-yl]acetate prepared in Example **10** (507.5 mg, 2.30 mmol), and 2-[5-methyl-2-(4-methylphenyl)-1,3-oxazol-4-yl]ethanol (500 mg, 2.30 mmol), TMAD (792.6 mg, 4.60 mmol), Ph_3P (1.21 g, 4.60 mmol) in 15 mL anhydrous DCM was stirred at rt under argon for 12 hours. DCM was removed under reduced pressure. Flash chromatograph of the residue over silica gel using 1% CH_3CN/ CH_2Cl_2 gave ethyl 2-((1*S*)-5-{2-[5-methyl-2-(4-methylphenyl)(1,3-oxazol-4-yl)]ethoxy}indanyl)acetate (776.3 mg, 1.85 mmol, 80.5%). HPLC/MS $(M+H)^+$ m/z 420.5.

[058] **EXAMPLE 12**

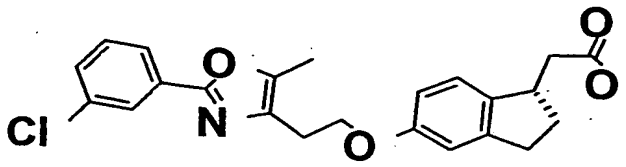
Preparation of 2-{(1*S*)-5-{2-[5-methyl-2-(4-methylphenyl)(1,3-oxazol-4-yl)]ethoxy}indanyl)acetic acid

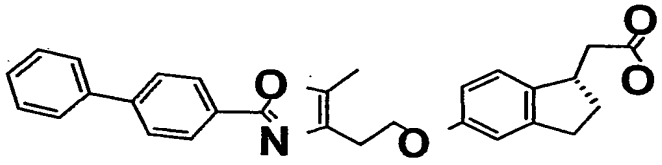


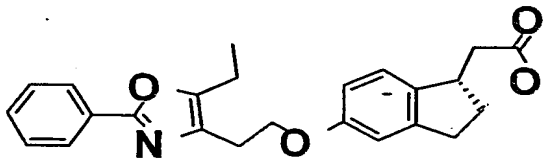
[059] Ethyl 2-((1*S*)-5-{2-[5-methyl-2-(4-methylphenyl)(1,3-oxazol-4-yl)]ethoxy}indanyl)acetate (Example **11**, 776.3 mg, 1.85 mmol) in THF (4.0 ml) was added to a mixture of aqueous LiOH (2 M, 3.7 ml, 7.4 mmol), water (2.0 ml), and EtOH (4.0 ml) at rt. The resulting mixture turned cloudy. This mixture was heated at 40°C (oil-bath temperature). The reaction was completed after 1.5 hours. After cooling to rt, 1 N HCl solution was slowly added to the mixture until pH 4.0. The compound was extracted with EtOAc (3 x 20 ml). The combined EtOAc layers were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue gave 2-((1*S*)-5-{2-[5-methyl-2-(4-methylphenyl)(1,3-oxazol-4-yl)]ethoxy}indanyl)acetic acid (616.8 mg, 1.57 mmol, 85%) as a white solid. ^{1}H NMR ($CDCl_3$) δ 7.83(d, 2H), 7.21(d, 2H), 7.03(d, 1H), 6.74(d, 1H),

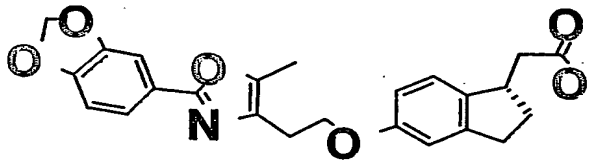
6.69(dd, 1H), 4.19(t, 2H), 3.45(q, 1H), 2.93(t, 2H), 2.78(m, 2H), 2.51(m, 2H), 2.30(s, 3H), 2.25(s, 3H), 1.53(m, 2H).

[060] By using the methods described above for Examples **1-12** and by substituting the appropriate starting materials, the following compounds were similarly prepared.









Pharmaceutical Compositions

[061] Based on the assays described herein, or other well known assays used to determine the efficacy for treatment of conditions identified above in mammals, and by comparison of these results with the results of known medicaments that are used to treat these conditions, the effective dosage of a compound of this invention can readily be determined for treatment of each desired indication. The amount of the active ingredient to be administered in the treatment of one of these conditions can vary widely according to such considerations as the particular compound and dosage unit employed, the mode of administration, the period of treatment, the age and sex of the subject treated, and the nature and extent of the condition treated.

[062] The total amount of the active ingredient to be administered may generally range from about 0.001 mg/kg to about 200 mg/kg, and preferably from about 0.01 mg/kg to about 200 mg/kg body weight per day. A unit dosage may contain from about 0.05 mg to about 1500 mg of active ingredient, and may be administered one or more times per day. The daily dosage for administration by injection, including intravenous, intramuscular, subcutaneous, and parenteral injections, and use of infusion techniques may be from about 0.01 to about 200 mg/kg. The daily rectal dosage regimen may be from 0.01 to 200 mg/kg of total body weight. The transdermal concentration may be that required to maintain a daily dose of from 0.01 to 200 mg/kg.

[063] Of course, the specific initial and continuing dosage regimen for each subject will vary according to the nature and severity of the condition as determined by the attending diagnostician, the activity of the specific compound employed, the age of the subject, the diet of the subject, time of administration, route of administration, rate of excretion of the drug, drug combinations, and the like. The desired mode of treatment and number of doses of a compound of the present invention may be ascertained by those skilled in the art using conventional treatment tests.

[064] A compound of this invention may be utilized to achieve the desired pharmacological effect by administration to a subject in need thereof in an appropriately formulated pharmaceutical composition. A subject, for the purpose of this invention, is a mammal such as rodents, primates including humans, sheep, canines, felines, bovines, and swine, in need of treatment for a particular condition or disease. Therefore, the present invention includes pharmaceutical compositions which are comprised of a pharmaceutically acceptable carrier and a pharmaceutically effective amount of a compound as described herein. A pharmaceutically acceptable carrier is any carrier which is relatively non-toxic and innocuous to a subject at concentrations consistent with

effective activity of the active ingredient so that any side effects ascribable to the carrier do not vitiate the beneficial effects of the active ingredient. A pharmaceutically effective amount of a compound is that amount which produces a result or exerts an influence on the particular condition being treated. A compound as described herein may be administered with a pharmaceutically-acceptable carrier using any effective conventional dosage unit forms, including, for example, immediate and timed release preparations, orally, parenterally, topically, or the like.

[065] For oral administration, the compound may be formulated into solid or liquid preparations such as, for example, capsules, pills, tablets, troches, lozenges, melts, powders, solutions, suspensions, or emulsions, and may be prepared according to methods known to the art for the manufacture of pharmaceutical compositions. The solid unit dosage forms may be a capsule which can be of the ordinary hard- or soft-shelled gelatin type containing, for example, surfactants, lubricants, and inert fillers such as lactose, sucrose, calcium phosphate, and corn starch.

[066] In another embodiment, the compound of this invention may be tableted with conventional tablet bases such as lactose, sucrose, and cornstarch in combination with binders such as acacia, cornstarch, or gelatin; disintegrating agents intended to assist the break-up and dissolution of the tablet following administration such as potato starch, alginic acid, corn starch, and guar gum; lubricants intended to improve the flow of tablet granulation and to prevent the adhesion of tablet material to the surfaces of the tablet dies and punches, for example, talc, stearic acid, or magnesium, calcium or zinc stearate; dyes; coloring agents; and flavoring agents intended to enhance the aesthetic qualities of the tablets and make them more acceptable to the subject. Suitable excipients for use in oral liquid dosage forms include diluents such as water and alcohols, for example, ethanol, benzyl alcohol, and polyethylene alcohols, either with or without the addition of a pharmaceutically acceptable surfactant, suspending agent, or emulsifying agent. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance tablets, pills or capsules may be coated with shellac, sugar or both.

[067] Dispersible powders and granules are suitable for the preparation of an aqueous suspension. They provide the active ingredient in admixture with a dispersing or wetting agent, a suspending agent, and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example, those sweetening, flavoring and coloring agents described above, may also be present.

[068] The pharmaceutical compositions of this invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil such as liquid paraffin or a mixture of vegetable oils. Suitable emulsifying agents may be (1) naturally occurring gums such as gum acacia and gum tragacanth, (2) naturally occurring phosphatides such as soy bean and lecithin, (3) esters or partial esters derived from fatty acids and hexitol anhydrides, for example, sorbitan monooleate, and (4) condensation products of said partial esters with ethylene oxide, for example, polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

[069] Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil such as, for example, arachis oil, olive oil, sesame oil, or coconut oil; or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent such as, for example, beeswax, hard paraffin, or cetyl alcohol. The suspensions may also contain one or more preservatives, for example, ethyl or *n*-propyl p-hydroxybenzoate; one or more coloring agents; one or more flavoring agents; and one or more sweetening agents such as sucrose or saccharin.

[070] Syrups and elixirs may be formulated with sweetening agents such as, for example, glycerol, propylene glycol, sorbitol, or sucrose. Such formulations may also contain a demulcent, and preservative, flavoring and coloring agents.

[071] The compound of this invention may also be administered parenterally, that is, subcutaneously, intravenously, intramuscularly, or interperitoneally, as injectable dosages of the compound in a physiologically acceptable diluent with a pharmaceutical carrier which may be a sterile liquid or mixture of liquids such as water, saline, aqueous dextrose and related sugar solutions; an alcohol such as ethanol, isopropanol, or hexadecyl alcohol; glycols such as propylene glycol or polyethylene glycol; glycerol ketals such as 2,2-dimethyl-1,1-dioxolane-4-methanol, ethers such as poly(ethyleneglycol) 400; an oil; a fatty acid; a fatty acid ester or glyceride; or an acetylated fatty acid glyceride with or without the addition of a pharmaceutically acceptable surfactant such as a soap or a detergent, suspending agent such as pectin, carbomers, methycellulose, hydroxypropylmethylcellulose, or carboxymethylcellulose, or emulsifying agent and other pharmaceutical adjuvants.

[072] Illustrative of oils which can be used in the parenteral formulations of this invention are those of petroleum, animal, vegetable, or synthetic origin, for example, peanut oil, soybean oil, sesame oil, cottonseed oil, corn oil, olive oil, petrolatum, and mineral oil. Suitable fatty acids include oleic acid, stearic acid, and isostearic acid. Suitable fatty acid esters are, for example, ethyl oleate and isopropyl myristate. Suitable soaps include fatty

alkali metal, ammonium, and triethanolamine salts and suitable detergents include cationic detergents, for example, dimethyl dialkyl ammonium halides, alkyl pyridinium halides, and alkylamine acetates; anionic detergents, for example, alkyl, aryl, and olefin sulfonates, alkyl, olefin, ether, and monoglyceride sulfates, and sulfosuccinates; nonionic detergents, for example, fatty amine oxides, fatty acid alkanolamides, and polyoxyethylenepolypropylene copolymers; and amphoteric detergents, for example, alkyl-beta-aminopropionates, and 2-alkylimidazoline quarternary ammonium salts, as well as mixtures.

[073] The parenteral compositions of this invention may typically contain from about 0.5% to about 25% by weight of the active ingredient in solution. Preservatives and buffers may also be used advantageously. In order to minimize or eliminate irritation at the site of injection, such compositions may contain a non-ionic surfactant having a hydrophile-lipophile balance (HLB) of from about 12 to about 17. The quantity of surfactant in such formulation ranges from about 5% to about 15% by weight. The surfactant can be a single component having the above HLB or can be a mixture of two or more components having the desired HLB.

[074] Illustrative of surfactants used in parenteral formulations are the class of polyethylene sorbitan fatty acid esters, for example, sorbitan monooleate and the high molecular weight adducts of ethylene oxide with a hydrophobic base, formed by the condensation of propylene oxide with propylene glycol.

[075] The pharmaceutical compositions may be in the form of sterile injectable aqueous suspensions. Such suspensions may be formulated according to known methods using suitable dispersing or wetting agents and suspending agents such as, for example, sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethyl-cellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents which may be a naturally occurring phosphatide such as lecithin, a condensation product of an alkylene oxide with a fatty acid, for example, polyoxyethylene stearate, a condensation product of ethylene oxide with a long chain aliphatic alcohol, for example, heptadecaethyleneoxycetanol, a condensation product of ethylene oxide with a partial ester derived form a fatty acid and a hexitol such as polyoxyethylene sorbitol monooleate, or a condensation product of an ethylene oxide with a partial ester derived from a fatty acid and a hexitol anhydride, for example polyoxyethylene sorbitan monooleate.

[076] The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent. Diluents and solvents that may be employed are, for example, water, Ringer's solution, and isotonic

sodium chloride solution. In addition, sterile fixed oils are conventionally employed as solvents or suspending media. For this purpose, any bland, fixed oil may be employed including synthetic mono or diglycerides. In addition, fatty acids such as oleic acid may be used in the preparation of injectables.

[077] A composition of the invention may also be administered in the form of suppositories for rectal administration of the drug. These compositions may be prepared by mixing the drug with a suitable non-irritation excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such material are, for example, cocoa butter and polyethylene glycol.

[078] Another formulation employed in the methods of the present invention employs transdermal delivery devices ("patches"). Such transdermal patches may be used to provide continuous or discontinuous infusion of the compounds of the present invention in controlled amounts. The construction and use of transdermal patches for the delivery of pharmaceutical agents is well known in the art (*see,* e.g., U.S. Patent No. 5,023,252, incorporated herein by reference). Such patches may be constructed for continuous, pulsatile, or on demand delivery of pharmaceutical agents.

[079] It may be desirable or necessary to introduce the pharmaceutical composition to the subject via a mechanical delivery device. The construction and use of mechanical delivery devices for the delivery of pharmaceutical agents is well known in the art. For example, direct techniques for administering a drug directly to the brain usually involve placement of a drug delivery catheter into the subject's ventricular system to bypass the blood-brain barrier. One such implantable delivery system, used for the transport of agents to specific anatomical regions of the body, is described in U.S. Patent No. 5,011,472, incorporated herein by reference.

[080] The compositions of the invention may also contain other conventional pharmaceutically acceptable compounding ingredients, generally referred to as carriers or diluents, as necessary or desired. Any of the compositions of this invention may be preserved by the addition of an antioxidant such as ascorbic acid or by other suitable preservatives. Conventional procedures for preparing such compositions in appropriate dosage forms can be utilized.

[081] Commonly used pharmaceutical ingredients which may be used as appropriate to formulate the composition for its intended route of administration include: acidifying agents, for example, but are not limited to, acetic acid, citric acid, fumaric acid, hydrochloric acid, nitric acid; and alkalinizing agents such as, but are not limited to, ammonia solution, ammonium carbonate, diethanolamine, monoethanolamine, potassium

hydroxide, sodium borate, sodium carbonate, sodium hydroxide, triethanolamine, trolamine.

[082] Other pharmaceutical ingredients include, for example, but are not limited to, adsorbents (e.g., powdered cellulose and activated charcoal); aerosol propellants (e.g., carbon dioxide, CCl_2F_2, F_2ClC–$CClF_2$ and $CClF_3$); air displacement agents (e.g., nitrogen and argon); antifungal preservatives (e.g., benzoic acid, butylparaben, ethylparaben, methylparaben, propylparaben, sodium benzoate); antimicrobial preservatives (e.g., benzalkonium chloride, benzethonium chloride, benzyl alcohol, cetylpyridinium chloride, chlorobutanol, phenol, phenylethyl alcohol, phenylmercuric nitrate and thimerosal); antioxidants (e.g., ascorbic acid, ascorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, hypophosphorus acid, monothioglycerol, propyl gallate, sodium ascorbate, sodium bisulfite, sodium formaldehyde sulfoxylate, sodium metabisulfite); binding materials (e.g., block polymers, natural and synthetic rubber, polyacrylates, polyurethanes, silicones and styrene-butadiene copolymers); buffering agents (e.g., potassium metaphosphate, potassium phosphate monobasic, sodium acetate, sodium citrate anhydrous and sodium citrate dihydrate); carrying agents (e.g., acacia syrup, aromatic syrup, aromatic elixir, cherry syrup, cocoa syrup, orange syrup, syrup, corn oil, mineral oil, peanut oil, sesame oil, bacteriostatic sodium chloride injection and bacteriostatic water for injection); chelating agents (e.g., edetate disodium and edetic acid); colorants (e.g., FD&C Red No. 3, FD&C Red No. 20, FD&C Yellow No. 6, FD&C Blue No. 2, D&C Green No. 5, D&C Orange No. 5, D&C Red No. 8, caramel and ferric oxide red); clarifying agents (e.g., bentonite); emulsifying agents (but are not limited to, acacia, cetomacrogol, cetyl alcohol, glyceryl monostearate, lecithin, sorbitan monooleate, polyethylene 50 stearate); encapsulating agents (e.g., gelatin and cellulose acetate phthalate); flavorants (e.g., anise oil, cinnamon oil, cocoa, menthol, orange oil, peppermint oil and vanillin); humectants (e.g., glycerin, propylene glycol and sorbitol); levigating agents (e.g., mineral oil and glycerin); oils (e.g., arachis oil, mineral oil, olive oil, peanut oil, sesame oil and vegetable oil); ointment bases (e.g., lanolin, hydrophilic ointment, polyethylene glycol ointment, petrolatum, hydrophilic petrolatum, white ointment, yellow ointment, and rose water ointment); penetration enhancers (transdermal delivery) (e.g., monohydroxy or polyhydroxy alcohols, saturated or unsaturated fatty alcohols, saturated or unsaturated fatty esters, saturated or unsaturated dicarboxylic acids, essential oils, phosphatidyl derivatives, cephalin, terpenes, amides, ethers, ketones and ureas); plasticizers (e.g., diethyl phthalate and glycerin); solvents (e.g., alcohol, corn oil, cottonseed oil, glycerin, isopropyl alcohol, mineral oil, oleic acid, peanut oil, purified water, water for injection, sterile water for injection and sterile water for

irrigation); stiffening agents (e.g., cetyl alcohol, cetyl esters wax, microcrystalline wax, paraffin, stearyl alcohol, white wax and yellow wax); suppository bases (e.g., cocoa butter and polyethylene glycols (mixtures)); surfactants (e.g., benzalkonium chloride, nonoxynol 10, oxtoxynol 9, polysorbate 80, sodium lauryl sulfate and sorbitan monopalmitate); suspending agents (e.g., agar, bentonite, carbomers, carboxymethylcellulose sodium, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, kaolin, methylcellulose, tragacanth and veegum); sweetening e.g., aspartame, dextrose, glycerin, mannitol, propylene glycol, saccharin sodium, sorbitol and sucrose); tablet anti-adherents (e.g., magnesium stearate and talc); tablet binders (e.g., acacia, alginic acid, carboxymethylcellulose sodium, compressible sugar, ethylcellulose, gelatin, liquid glucose, methylcellulose, povidone and pregelatinized starch); tablet and capsule diluents (e.g., dibasic calcium phosphate, kaolin, lactose, mannitol, microcrystalline cellulose, powdered cellulose, precipitated calcium carbonate, sodium carbonate, sodium phosphate, sorbitol and starch); tablet coating agents (e.g., liquid glucose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, methylcellulose, ethylcellulose, cellulose acetate phthalate and shellac); tablet direct compression excipients (e.g., dibasic calcium phosphate); tablet disintegrants (e.g., alginic acid, carboxymethylcellulose calcium, microcrystalline cellulose, polacrillin potassium, sodium alginate, sodium starch glycollate and starch); tablet glidants (e.g., colloidal silica, corn starch and talc); tablet lubricants (e.g., calcium stearate, magnesium stearate, mineral oil, stearic acid and zinc stearate); tablet/capsule opaquants (e.g., titanium dioxide); tablet polishing agents (e.g., carnuba wax and white wax); thickening agents (e.g., beeswax, cetyl alcohol and paraffin); tonicity agents (e.g., dextrose and sodium chloride);viscosity increasing agents (e.g., alginic acid, bentonite, carbomers, carboxymethylcellulose sodium, methylcellulose, povidone, sodium alginate and tragacanth); and wetting agents (e.g., heptadecaethylene oxycetanol, lecithins, polyethylene sorbitol monooleate, polyoxyethylene sorbitol monooleate, and polyoxyethylene stearate).

[083] The compound as described herein may be administered as the sole pharmaceutical agent or in combination with one or more other pharmaceutical agents where the combination causes no unacceptable adverse effects. For example, the compound of this invention can be combined with known anti-obesity, or with known antidiabetic or other indication agents, and the like, as well as with admixtures and combinations thereof.

[084] The compound as described herein may also be utilized, in free base form or in compositions, in research and diagnostics, or as analytical reference standards, and the like. Therefore, the present invention includes compositions which are comprised of an

inert carrier and an effective amount of a compound identified by the methods described herein, or a salt or ester thereof. An inert carrier is any material which does not interact with the compound to be carried and which lends support, means of conveyance, bulk, traceable material, and the like to the compound to be carried. An effective amount of compound is that amount which produces a result or exerts an influence on the particular procedure being performed.

[085] Formulations suitable for subcutaneous, intravenous, intramuscular, and the like; suitable pharmaceutical carriers; and techniques for formulation and administration may be prepared by any of the methods well known in the art (*see, e.g.,* Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pa., 20th edition, 2000).

[086] The following examples are presented to illustrate the invention described herein, but should not be construed as limiting the scope of the invention in any way.

[087] Capsule Formulation

A capsule formula is prepared from:

Compound of this invention	40 mg
Starch	109 mg
Magnesium stearate	1 mg

The components are blended, passed through an appropriate mesh sieve, and filled into hard gelatin capsules.

[088] Tablet Formulation

A tablet is prepared from:

Compound of this invention	25 mg
Cellulose, microcrystaline	200 mg
Colloidal silicon dioxide	10 mg
Stearic acid	5.0 mg

The ingredients are mixed and compressed to form tablets. Appropriate aqueous and non-aqueous coatings may be applied to increase palatability, improve elegance and stability or delay absorption.

[089] Sterile IV Solution

A 5 mg/ml solution of the desired compound of this invention is made using sterile, injectable water, and the pH is adjusted if necessary. The solution is diluted for administration to 1-2 mg/ml with sterile 5% dextrose and is administered as an IV infusion over 60 minutes.

[090] Intramuscular suspension

The following intramuscular suspension is prepared:

Compound of this invention	50 mg/ml
Sodium carboxymethylcellulose	5 mg/ml
TWEEN 80	4 mg/ml
Sodium chloride	9 mg/ml
Benzyl alcohol	9 mg/ml

The suspension is administered intramuscularly.

[091] Hard Shell Capsules

A large number of unit capsules are prepared by filling standard two-piece hard galantine capsules each with 100 mg of powdered active ingredient, 150 mg of lactose, 50 mg of cellulose and 6 mg of magnesium stearate.

[092] Soft Gelatin Capsules

A mixture of active ingredient in a digestible oil such as soybean oil, cottonseed oil or olive oil is prepared and injected by means of a positive displacement pump into molten gelatin to form soft gelatin capsules containing 100 mg of the active ingredient. The capsules are washed and dried. The active ingredient can be dissolved in a mixture of polyethylene glycol, glycerin and sorbitol to prepare a water miscible medicine mix.

[093] Immediate Release Tablets/Capsules

These are solid oral dosage forms made by conventional and novel processes. These units are taken orally without water for immediate dissolution and delivery of the medication. The active ingredient is mixed in a liquid containing ingredient such as sugar, gelatin, pectin and sweeteners. These liquids are solidified into solid tablets or caplets by freeze drying and solid state extraction techniques. The drug compounds may be compressed with viscoelastic and thermoelastic sugars and polymers or effervescent components to produce porous matrices intended for immediate release, without the need of water.

EXAMPLES

[094] Demonstration of the activity of a compound may be accomplished through *in vitro*, *ex vivo*, and *in vivo* assays that are well known in the art. For example, to demonstrate the efficacy of a pharmaceutical agent for the treatment of diabetes and related disorders such as Syndrome X, impaired glucose tolerance, impaired fasting glucose, and hyperinsulinemia or atherosclerotic disease and related disorders such as hypertriglyceridemia and hypercholesteremia, the following assays may be used.

Example 1: Insulin Receptor Binding in 3T3-L1 Cells Treated with Compounds

[095] 3T3-L1 cells were seeded at 9300 cells per well in Costar flat bottom TC and incubated for 1 week until they were 2 days post-confluent. The cells were then treated for 2 days with differentiation media (Dulbecco's Modified Eagle Medium (DMEM),100 µg/ml Penicillin/Streptomycin, 2 mM L-Glutamine, 10% Fetal Bovine Serum) containing 0.5 µM human Insulin-like Growth Factor (IGF-1) and test compounds. After treatment, the media was replaced with differentiation media, and the cells were incubated for 4 days. The cells were then assayed for insulin receptor activity. After washing the cells with buffer, they were incubated with 0.1 nM ^{125}I-insulin and (+/-) 100 nM unlabeled insulin, and incubated at rt for 1 hour. The cells were then washed 3x with buffer, dissolved with 1N NaOH, and counted on a gamma counter. An EC50 value was determined if a plateau is attained and percent maximum stimulation is assessed.

Example 2: Method for Measuring Blood Glucose Levels

[096] The following method may be used to identify a compound that has glucose lowering activity. db/db mice were bled (by either eye or tail vein) and grouped according to equivalent mean blood glucose levels. They were dosed orally (by gavage in a pharmaceutically acceptable vehicle) with the test compound or control (e.g., vehicle only) once daily for 7 days. On day 8, the animals were bled again by eye or tail vein and blood glucose levels were determined. In each case, glucose levels were measured with a Glucometer Elite XL (Bayer Corporation, Elkhart, IN), and the glucose levels of control vs. treated animals were compared.

Example 3: Method for Measuring Triglyceride Levels

[097] The following method may be used to identify a compound that has triglyceride lowering activity. hApoA1 mice were bled (by either eye or tail vein) and grouped according to equivalent mean serum triglyceride levels. They were dosed orally (by gavage in a pharmaceutically acceptable vehicle) with the test compound or control (e.g.,

vehicle only) once daily for 7 days. The animals were then bled by eye or tail vein on day 8, and serum triglyceride levels were determined. In each case, triglyceride levels were measured using a Technicon Axon Autoanalyzer (Bayer Corporation, Tarrytown, NY), and the triglyceride levels of control vs. treated animals were compared.

Example 4: Method for Measuring HDL-Cholesterol Levels

[098] To identify a compound that increased plasma HDL-cholesterol levels, hApoA1 mice are bled and grouped with equivalent mean plasma HDL-cholesterol levels. The mice are orally dosed once daily with vehicle or test compound or control (e.g., vehicle) for 7 days, and then bled again on day 8. Plasma is analyzed for HDL-cholesterol using the Synchron Clinical System (CX4) (Beckman Coulter), and plasma HDL-cholesterol levels of control vs. treated animals were compared.

Example 5: Method for Measuring Total Cholesterol, HDL-Cholesterol, Triglycerides, and Glucose Levels

[099] In another *in vivo* assays, obese monkeys are bled, then orally dosed once daily with vehicle or test compound for 4 weeks, and then bled again. Serum is analyzed for total cholesterol, HDL-cholesterol, triglycerides, and glucose using the Synchron Clinical System (CX4) from Beckman Coulter. Lipoprotein subclass analysis is performed by NMR spectroscopy as described by Oliver et al., (PNAS 98(9):5306-5311, 2001).

Example 6: Method for Measuring an Effect on Cardiovascular Parameters

[100] Cardiovascular parameters (e.g., heart rate and blood pressure) are also monitored. SHR rats are orally dosed once daily with vehicle or test compound for 2 weeks. Blood pressure and heart rate are determined using a tail-cuff method as described by Grinsell et al., (Am. J. Hypertens. 13(4):370-375, 2000). In monkeys, blood pressure and heart rate are monitored as described by Shen et al., (J. Pharmacol. Exp. Therap. 278(3):1435-1443, 1996).

[101] It should be apparent to one of ordinary skill in the art that changes and modifications can be made to this invention without departing from the spirit or scope of the invention as it is set forth herein.

We claim:

1. A method of treating diabetes and diabetes-related disorders comprising the step of administering to a subject in need thereof a pharmaceutically effective amount of a compound which has glucose-lowering activity, triglyceride-lowering activity, and increases HDL levels.

2. The method of claim 1, wherein said diabetes-related disorder is selected from the group consisting of hyperglycemia, hyperinsulinemia, impaired glucose tolerance, impaired fasting glucose, dyslipidemia, hypertriglyceridemia, Syndrome X, insulin resistance, obesity, atherosclerotic disease, hyperlipidemia, hypercholesteremia, low HDL levels, hypertension, cardiovascular disease, cerebrovascular disease, peripheral vessel disease, lupus, polycystic ovary syndrome, carcinogenesis, and hyperplasia.

3. The method of claim 1, wherein said subject is a mammal.

4. The method of claim 3, wherein said mammal is selected from the group consisting of rodents, primates, sheep, canines, felines, bovines, and swine.

5. The method of claim 4, wherein said mammal is human.

6. The method of claim 1 comprising the step of administering to a subject in need thereof a pharmaceutically effective amount of a compound which has glucose-lowering activity, triglyceride-lowering activity, and increases HDL levels in combination with one or more hypoglycemic agents.

7. The method of claim 1 comprising the step of administering to a subject in need thereof a pharmaceutically effective amount of a compound which has glucose-lowering activity, triglyceride-lowering activity, and increases HDL levels in combination with one or more agents selected from the group consisting of HMG CoA reductase inhibitor, bile acid binding agent, fibric acid derivative, agent that regulates hypertension, and agent that regulates body weight.

8. A pharmaceutical composition comprising an effective amount of a compound which has glucose-lowering activity, triglyceride-lowering activity, and increases

HDL levels with a pharmaceutically acceptable carrier.

9. A pharmaceutical composition comprising an effective amount of a compound which has glucose-lowering activity, triglyceride-lowering activity, and increases HDL levels in combination with a pharmaceutically acceptable carrier and one or more hypoglycemic agents.

10. A pharmaceutical composition comprising an effective amount of a compound which has glucose-lowering activity, triglyceride-lowering activity, and increases HDL levels in combination with a pharmaceutically acceptable carrier and one or more agents selected from the group consisting of HMG CoA reductase inhibitor, bile acid binding agent, fibric acid derivative, agent that regulates hypertension, and agent that regulates body weight.

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Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations*

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(54) Title: METHOD OF TREATING DIABETES AND DIABETES-RELATED DISORDERS

(57) Abstract: This invention relates to a method of treating diabetes and diabetes-related disorders. Specifically, the method of the present invention relates to administering a single compound that lowers blood glucose levels, lowers serum triglyceride levels, and increases serum high density lipoproteins (HDL) levels thereby providing a treatment option for individuals afflicted with a metabolic disorder such as diabetes mellitus, insulin resistance, impaired glucose tolerance, and dyslipidemia.

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A. CLASSIFICATION OF SUBJECT MATTER
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B. FIELDS SEARCHED

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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X — Y	US 6,028,052 A (HEYMAN et al) 22 February 2000 (22.02.2000) abstract, column 1, lines 60-67, columns 3-4.	1-6, 8, 9 — 7, 10

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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